EDITORIAL COMMENT
From the Atomic Nucleus to Man
Nuclear Magnetic Resonance Spectroscopy, the Next Horizon in Diagnostic Cardiology*
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The study by Nakae et al. (1) in this issue of the Journal presents compelling evidence suggesting a role for (nuclear) magnetic resonance (MR) spectroscopy to assess heart failure in the future. No longer relegated clinically to only providing finely detailed anatomical images, the full potential of MR techniques is the ability to visualize biochemical and physiological processes. With respect to physiologic processes, it is the ability of MR to rapidly image ventricular volumes and wall motion, to evaluate viability, to assess arterial morphology and plaque, and to evaluate myocardial perfusion. In the case of biochemical processes, it is the ability of MR to perform spectroscopy and evaluate myocardial metabolism (without the use of radionuclides).

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Unlike phosphorus (31P) or sodium (23Na) protons, the hydrogen nucleus, or 1H, can be very sensitively detected by MR spectroscopic methods. The proton has the highest magnetic moment of all biologically relevant nuclei. As a result, the volume of interest that is interrogated can be smaller, and the confounding influence of signals from outside this volume can be minimized. In addition, the increased sensitivity of the hydrogen nucleus means that the entire heart can be evaluated, not just the anterior and anteroseptal walls of the left ventricle, as is presently the case with clinical phosphorus spectroscopy to evaluate myocardial high-energy phosphate metabolism.

The role of myocardial phosphocreatine (PCr) as an energy shuttle (2,3) remains somewhat controversial. Recent proponents argue for a role of PCr in the transfer of energy from the mitochondria to the myofibrils under conditions of high workload (4,5), while others point to the functional stability of hearts from transgenic mice without creatine phosphokinase (CPK) (6) and the diffusional mobility of PCr being equivalent to that of adenosine triphosphate (ATP). However, there is no doubt that PCr serves as a storage depot for ATP repletion during times of stress. This reaction, which repletes ATP, is normally at equilibrium in myocardial cells, and the reaction proceeds as the result of mass action—that is, the concentrations of the reactive products determine the steady-state concentrations that result. As ATP is hydrolyzed to adenosine diphosphate (ADP), the increased concentration of ADP drives the reaction to favor the hydrolysis of PCr to creatine to regenerate the ATP. Likewise, alterations in the concentration of creatine directly impact the resulting concentrations of PCr—more creatine means more PCr, whereas less creatine means less PCr (in the resting state). The impact of a lower PCr concentration is evident, especially under conditions of metabolic stress or ischemia. However, the preponderance of clinical measures of PCr and ATP rely upon the ratio of these two important bioenergetic molecules. Because this relationship is close to equilibrium, changes in the ratio only occur when the myocardium undergoes rapid change in energy utilization. In contrast, quantitative measurement of the metabolites under the same conditions may reveal a decline in the pool sizes and a significant decline in the ability of the myocardium to survive periods of ischemia.

Although MR spectroscopic techniques hold great clinical promise, they have not found widespread application. The application of 1H spectroscopy to the heart has provided a means to quantitate myocardial lipids. In this scenario increased concentrations of lipid provide evidence of myocardial ischemia vis-à-vis the inability to aerobically metabolize lipids (7). However, because the heart is generally bathed in a pool of similar lipids, the lipid in the myocardial walls adjacent to the pericardial fat is presently difficult to assess. Only the interventricular septum is free of the confounding effects of the pericardial lipid. Research models have used 1H spectroscopy to assess the oxygenation status of myocardial myoglobin in an effort to determine the severity of an ischemic event (8,9), but this has not yet been clinically applied. Recent work by Bottomley and coworkers (10) showed decreased concentrations of creatine in areas of infarcted myocardium using 1H spectroscopy, although the progression of creatine loss as a function of the stage of infarction was not possible in their study. Although recent results using 31P-NMR spectroscopy at rest and with stress have suggested that this technique has the ability to identify myocardial ischemia in the absence of epicardial coronary artery disease, perhaps at the microvascular level (11), and the presence of such stress-induced data portend a worse prognosis in women with chest pain, further data are needed before this approach can become a routine clinical procedure. Advances in MR scanner hardware have now made possible the simultaneous acquisition of 31P spectra with either 1H imaging or spectroscopy, thus decreasing the time required for these investigations and making new information available to the clinician.

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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The finding that the severity of a cardiomyopathy appears to be inversely correlated with the amount of creatine poses an interesting question—does the decrease in creatine cause (or hasten) the progression of the underlying myocardial pathology? Or, does the decline in creatine concentration simply provide a correlative observation? Although the investigators conclude that noninvasive assessment of myocardial creatine by $^1$H spectroscopy is useful for the assessment of the severity of heart failure associated with cardiomyopathy (1), this role might be best served by high-resolution MR imaging to evaluate ventricular wall motion, ejection fraction, and volumes. Alternatively, the findings from the current study (1) suggest the possibility of the biochemical as opposed to the functional staging of heart failure. Our own conclusions from this study are that PCr and creatine may play a substantial causative role underlying the progression of heart failure in cardiomyopathy. More importantly, the study by Nakae et al. (1) has demonstrated the ability of MR methods to traverse the enormous space from the atomic nucleus (the protons of creatine) to man (the progression of heart failure associated with cardiomyopathy).

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